DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission of RCE filed on November 24, 2008 and the amendment filed on January 9, 2009 have been entered. The claims pending in this application are claims 91-102, 104, 110-119, 122 and 123. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on January 9, 2009.

Information Disclosure Statement

2. 1449 form filed on November 25, 2008 has been considered and signed. This 1449 form was used to replace the 1449 form filed on March 13, 2008 by applicant.

Claim Objections

3. Claim 101 is objected to because of the following informality: "T7, T3, SP6" should be "T7 RNA polymerase, T3 RNA polymerase, SP6 RNA polymerase".

4. Claim 113 or 114 or 115 or 116 is objected to because of the following informality: "said protein coding sense RNA" should be "said protein coded by said sense RNA".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Scope of Enablement

Claims 91-102, 104, 110-119, 122, and 123 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a specific nucleic acid comprising a sequence coding for a protein in a cell *in vitro* by introducing a conjugate formed by T7 RNA polymerase and a vector containing a promoter for T7 RNA polymerase and said nucleic acid comprising a sequence coding for a protein wherein the promoter for T7 RNA polymerase is upstream of said nucleic acid comprising a sequence coding for a protein (ie., using said conjugate), does not reasonably provide enablement for producing a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 in any kind of cell *in vivo* by introducing a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into the cell (ie., using said conjugate recited in claims 91-102, 104, 110-119, 122, and 123). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

<u>The nature of the invention</u>

Claims 91-102, 104, 110-119, 122, and 123 is directed to a conjugate. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.,* 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The Breadth of The Claims

Claims 91-102 and 104 encompass a conjugate comprising a protein-nucleic acid construct that comprises at least one of any kind of promoter, at least one segment of a specific nucleic acid comprising a sequence coding for a protein and any kind of RNA polymerase wherein, when said conjugate is introduced into any kind of cell *in vivo*, the conjugate can produce said specific nucleic acid and said RNA polymerase is covalently linked to the nucleic acid of said protein-nucleic acid construct. Claims 110-118 encompass a conjugate comprising a protein-nucleic acid construct that comprises at least one of any kind of promoter, at least one segment of a specific nucleic acid comprising a template for transcription, and any kind of RNA polymerase wherein, when said conjugate is introduced into any kind of cell *in vivo*, said conjugate produces said specific nucleic acid and said RNA polymerase is covalently linked to the nucleic acid of said protein-nucleic acid construct. Claims 119, 122, 123 encompass a conjugate comprising a protein-nucleic acid construct that comprises at least one of any kind of promoter, at least one single-stranded segment comprising a sequence complementary to any kind of primer present in a cell and any kind of polymerase wherein, when said conjugate is introduced into said cell *in vivo*, the conjugate can produce a specific nucleic acid and said RNA polymerase is covalently linked to the nucleic acid of said protein-nucleic acid construct.

Working Examples

The specification provides working examples (see pages 43-63) for amplification of different DNAs and amplification from RNA template. The specification provides no working example for producing a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 in any kind of cell *in vivo* by introducing a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into the cell.

The Amount of Direction or Guidance Provided and The State of The Prior Art

Although the specification teaches a protein- nucleic acid complex formed by M13mp18 RF and DNA polymerase (see Example 3, pages 45 and 46), the specification does not provide a guidance for producing a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 in any kind of cell *in vivo* by introducing a conjugate recited in claims 91-102, 104, 110-119, 122, and 123. Furthermore, there is no experimental condition and/or experimental data in the specification to support the claimed invention. Although it is known in the art that T7 RNA polymerase RNA can be produced in a cell *in vitro* when a conjugate formed by T7 RNA polymerase and a vector containing T7 promoter and T7 RNA polymerase gene is introduced into the cell *in vitro* wherein T7 RNA polymerase gene is controlled by T7 promoter in the vector (see Wagner *et al.,* US Patent No. 5,591,601, see abstract, columns 2, 3, and 5), during the process of the prior art search, the examiner has not found any art which is related to produce a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 in any kind of cell *in vivo* by introducing a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into the cell.

Level of Skill in The Art, The Unpredictability of The Art, and The Quantity of Experimentation Necessary

While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 can be produced in any kind of cell *in vivo* by introducing a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into the cell.

First, it is known that RNA polymerase is used for synthesis RNA during transcription and the transcription includes initiation, elongation and termination, and begins with the binding of RNA polymerase to the promoter in the gene which is located on the upstream of the gene (see attached definition for "transcription" from Wikipedia, the free encyclopedia), since the claims do not require that the at least one promoter and the at least one segment of said specific nucleic acid comprising a sequence coding for a protein or at least one segment of a specific nucleic acid comprising a template for transcription or at least one single-stranded segment comprising a sequence complementary to a primer present in said cell are inside of a vector and the at least one promoter is upstream of the at least one segment of said specific nucleic acid comprising a sequence coding for a protein or at least one segment of a specific nucleic acid comprising a template for transcription or at least one single-stranded segment comprising a sequence complementary to a primer present in said cell in the vector, if the at least one promoter and the at least one segment of said specific nucleic acid comprising a sequence coding for a protein or at least one segment of a specific nucleic acid comprising a template for transcription or at least one single-stranded segment comprising a sequence complementary to a primer present in said cell are not inside of a vector but are complementary each other, it is unclear how

a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 can be produced by introducing a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into a cell.

Second, since the claim does not require that a conjugate is introduced into a cell *in vitro* and the specification does not provide a guidance to introduce a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into a cell *in vivo* such as a cell in human body and there are a number of differences between *in vitro* models and the *in vivo* situation (see White et al., Pharmacotherapy, 21, 292S-301S, 2001), it is unclear how a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 can be introduced into a cell *in vivo* such as a cell in human body so that a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 can be produced in human body.

Third, even through we assume that the at least one promoter and the at least one segment of said specific nucleic acid comprising a sequence coding for a protein or at least one segment of a specific nucleic acid comprising a template for transcription or at least one single-stranded segment comprising a sequence complementary to a primer present in said cell are inside of a vector and the at least one promoter is upstream of the at least one segment of said specific nucleic acid comprising a sequence coding for a protein or at least one segment of a specific nucleic acid comprising a template for transcription or at least one single-stranded segment comprising a sequence complementary to a primer present in said cell in the vector, since the claims do not require that the RNA polymerase is bacteriphage T7 RNA polymerase which is a RNA polymerase capable of carrying out transcription with high promoter specificity and efficiency without involvement of any cellular transcription factor (see page 2114, right column from Chen *et al.,* Nucleic Acids Research, 22, 2114-2120, 1994) and do not limit sources of the

cell and RNA polymerase, and it is known that other RNA polymerase such as RNA polymerase II can function only in the presence of cellular transcription factors (see Shilatifard *et al.,* Annu. Rev. Biochem.,72, 693-715, 2003 and attached definition for "RNA polymerase II" from Wikipedia, the free encyclopedia) and the mechanisms of RNA synthesis in prokaryotes and eukaryotes are totally different and prokaryotic transcription occurs in the cytoplasm while eukaryotic transcription is localized to the nucleus (see attached definitions for "transcription", "prokaryotic transcription", and "eukaryotic transcription" from Wikipedia, the free encyclopedia), it is unclear, if the RNA polymerase is not bacteriphage T7 RNA polymerase, how a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 can be produced in any kind of cell such as a prokaryotic cell by introducing a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into the cell when the RNA polymerase is an eukaryotic RNA polymerase in the absence of eukaryotic specific cellular transcription factors and how a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 can be produced in any kind of cell such as an eukaryotic cell by introducing a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into the cell when the RNA polymerase is a prokaryotic RNA polymerase in the absence of prokaryotic specific cellular transcription factors. Furthermore, since claims 91, 93-102, 104, 110-119, 122, and 123 do not require that the promoter contain an initiation site of the RNA polymerase, it is unclear how the RNA polymerase can initiate RNA synthesis so that a specific nucleic acid recited in claims 91, 93-102, 104, 110-119, 122, and 123 can be produced. In addition, since the claims do not require that said RNA polymerase is covalently linked to the at least one promoter and it is known that the transcription begins with the binding of RNA polymerase to the promoter in the gene which

is located on the upstream of the gene (see attached definition for "transcription" from Wikipedia, the free encyclopedia), if said RNA polymerase is not covalently linked to the at least one promoter but is covalently linked to other part of the nucleic acid of said protein-nucleic acid construct, it is unclear how the RNA polymerase can initiate RNA synthesis so that a specific nucleic acid recited in claims 91, 93-102, 104, 110-119, 122, and 123 can be produced.

In view of above discussions, the skilled artisan will have no way to predict the experimental results. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. The undue experimentation at least includes to test whether a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 can be produced in any kind of cell *in vivo* by introducing a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into the cell.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the art is high, the specification provides one with no guidance that leads one to claimed methods. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples related to the invention and the no teaching in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

In page 10, second paragraph bridging to page 13, last paragraph of applicant's remarks field on November 24, 2008, applicant argues that: (1) "although T7 polymerase is a polymerase that does not require other auxiliary proteins, it was pointed out in the Office Action that some other RNA polymerases do require these factors. However, this point is moot as long as the conjugate is introduced into a cell that has these factors present"; and (2) "[A]pplicants further note that the pending claims are directed to protein-nucleic acid conjugates not to methods of use. Further, the preamble to the pending claims states 'the conjugate, which when introduced into a cell..'. Thus, the claimed conjugates could be expressed in cells ex vivo and in vivo. Even assuming *arguendo* that the claimed conjugates could not be used in vivo, the claims are directed to the product itself not the method. The Examiner actually concedes that the claimed conjugates are enabling for 'in vitro' (ex vivo) use".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since the claims do not require that the RNA polymerase is bacteriphage T7 RNA polymerase which is a RNA polymerase capable of carrying out transcription with high promoter specificity and efficiency without involvement of any cellular transcription factor (see page 2114, right column from Chen *et al.,* Nucleic Acids Research, 22, 2114-2120, 1994) and do not limit sources of the cell and RNA polymerase, and it is known that other RNA polymerase such as RNA polymerase II can function only in the presence of cellular transcription factors (see Shilatifard *et al.,* Annu. Rev. Biochem.,72, 693-715, 2003 and attached definition for "RNA polymerase II" from Wikipedia, the free encyclopedia) and the mechanisms of RNA synthesis in prokaryotes and eukaryotes are totally different and prokaryotic transcription occurs in the cytoplasm while eukaryotic transcription is localized to the nucleus

(see attached definitions for "transcription", "prokaryotic transcription", and "eukaryotic transcription" from Wikipedia, the free encyclopedia), it is unclear, if the RNA polymerase is not bacteriphage T7 RNA polymerase, how a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 can be produced in any kind of cell such as a prokaryotic cell by introducing a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into the cell when the RNA polymerase is an eukaryotic RNA polymerase in the absence of eukaryotic specific cellular transcription factors and how a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 can be produced in any kind of cell such as an eukaryotic cell by introducing a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into the cell when the RNA polymerase is a prokaryotic RNA polymerase in the absence of prokaryotic specific cellular transcription factors. Second, although claims are directed to the product itself not the method, the rejected claims require that the conjugated has abilities to be introduced into a cell *in vitro* and *in vivo*. Since the specification does not provide a guidance to introduce a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 into a cell *in vivo* such as a cell in human body and there are a number of differences between *in vitro* models and the *in vivo* situation (see White et al., Pharmacotherapy, 21, 292S-301S, 2001), it is unclear how a conjugate recited in claims 91-102, 104, 110-119, 122, and 123 can be introduced into a cell *in vivo* such as a cell in human body so that a specific nucleic acid recited in claims 91-102, 104, 110-119, 122, and 123 can be produced in human body.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 101 and 104 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 101 is rejected as vague and indefinite. Since claim 91 only has one RNA polymerase, it is unclear why said RNA polymerase recited in the claim can comprise a combination of T7 RNA polymerase, T3 RNA polymerase, and SP6 RNA polymerase. Please clarify.

10. Claim 104 recites the limitation in "claim 103" of the claim. There is insufficient antecedent basis for this limitation in the claim because claim 103 has been deleted. Please clarify.

Conclusion

11. No claim is allowed.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on (571)272-0763.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Frank W Lu /
Primary Examiner, Art Unit 1634
August 14, 2009